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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/186,475	11/04/1998	ANNIE FONG	238/046	1830

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EXAMINER
HUNT, JENNIFER ELIZABETH

ART UNIT	PAPER NUMBER
1642	12

DATE MAILED: 11/26/2001

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
09/186,475	Fong et al.
Examiner	**Art Unit**
Jennifer Hunt	1642

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☐ Responsive to communication(s) filed on _____ .

2a) ☐ This action is **FINAL.** 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1-24 and 27-32* is/are pending in the application.

4a) Of the above, claim(s) *19-22, 27, and 32* is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *1-18, 23, 24, and 28-31* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15) ☒ Notice of References Cited (PTO-892)
16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). 4
18) ☐ Interview Summary (PTO-413) Paper No(s). _____
19) ☐ Notice of Informal Patent Application (PTO-152)
20) ☐ Other:

DETAILED ACTION

1. The examiner assigned to this application has changed. Please address future correspondence to Jennifer Hunt, Art Unit 1642.

Election/Restriction

2. Applicant's election of species (specifically set forth below), in Paper No. 11 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Applicant has elected the following species:

(A) Disease etiology - cell proliferation, specifically cancer

(B) Angiogenesis receptors - flk-1

(C) Antagonist - compound a (which is also known as SU 5416)

(D) Sample type - whole blood or fraction thereof

(E) Angiogenesis markers - protein phosphorylation by measuring a protein

(F) Assay type- antibody assay

(G) Specific assay - detection with antibodies

The search has not been extended because these species have been found in the prior art. Therefor claims 1-24, and 27-32 are pending in the application. Claims 19-22, 27, and 32 have

been withdrawn from consideration as being drawn to a non-elected species of invention. An action on the merits of claims 1-18, 23-24, and 28-31 follows herein.

Claim Rejections - 35 U.S.C. § 112

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claims 1-18, 23-24, and 28-31 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A. Claims 1-18, 23-24, and 28-31 are unclear in the recitation of "marker related to angiogenesis". The metes and bounds of a "marker related to angiogenesis" cannot be determined. It is not clear what would be considered "related to angiogenesis" and what would not, and therefor it is not possible to determine what would be considered a marker which meets the limitations of the claim. Further, is not clear that any or all of the markers specified in claims 15 and 16 are "related to angiogenesis" at all.

B. Claim 7 recites the limitation "said drug" in line 1. There is insufficient antecedent basis for this limitation in the claim.

C. Claim 7 is further unclear in the recitation of "or a pharmaceutically acceptable salt, ester, amide, prodrug, isomer, and metabolite thereof. It is not clear if the recitation intended that the compound is all of these variants, any combination of the variants, or one of the variants.

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 1-18, 23-24, and 28-31 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for monitoring markers known in the art to correlate to angiogenesis for the purpose of determining an effective does of an angiogenesis inhibitor, does not reasonably provide enablement for monitoring any and all "angiogenesis related markers" for the purpose of determine an effective dose of an angiogenesis inhibitor. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Factors to be considered in determining scope and enablement are: 1) quantity of experimentation necessary, 2) the amount of direction or guidance presented in the specification, 3) the presence or absence of working examples, 4) the nature of the invention, 5) the state of the prior art, 6) the relative skill of those in the art, 7) the predictability of the unpredictability of the art, and 8) the breadth of the claims (see Ex parte Forman, 230 USPQ 546, BPAI, 1986).

The claims are broadly drawn to a method of determining an efficacious dose of a compound administered to a subject for the purpose of modulating angiogenesis comprising administering the compound to a patient, monitoring a marker related to angiogenesis, constructing a standard curve, and determining the efficacious dose based on the standard curve.

The specification provides generalized theoretical teachings in which a limited number of markers (tissue factor, IL-8, urokinase and tPA) are measured using PCR or ELISA, and a standard curve is generated to determine how much of the marker is in the isolated sample after a patients have received some sort of unspecified drug treatment. In a second theoretical example, cells are isolated from a patient, then administered a Flk-1 antagonist *in vitro*, and then the cells are eventually lysed and a marker is measured.

Thus the specification fails to provide any guidance or objective evidence that any of the markers which are taught or suggested by the specification in fact correlate to angiogenesis.

Diagnosing and monitoring cancer is an extremely complex process. Often a single factor (such as monitoring a marker) is insufficient to provide an accurate assessment of tumor progress or regression. Further, often a single variable will provide some information about a primary tumor, but fail to provide information regarding metastasis. If the treatment efficacy of a drug is to be measured using a marker, that marker must be carefully selected to be specific and accurate for the determination of the treatment's efficacy. Determination of a dosage using such a marker is even more complex. The marker which is selected must be known to specifically correlate to the progression or regression of disease, taking into account not only tumor size, metastasis,

aggressiveness, etc., but also toxicity, quality of life of the patient, etc. (For general guidelines on some of the factors for determining drug dosage, see pages 33-37 of Fingl and Woodbury, The Pharmacological basis of Therapeutics, Chapter I). In the instant case, the method fails to account for any of these factors. Further there is no guidance or objective evidence that the broadly recited markers correlate to progression or regression of any cancer, and thus there is no correlation of the broad range of markers to any type of cancer. Further, the most relevant example provided by the specification (that of a Flk-1 antagonist) refers to an *in vitro* test, which never involves administration of any compound to a patient. Thus it is not clear from applicant's teachings or examples that any marker correlates accurately enough to cancer progression such that it would be effective for determine a dosage curve for a patient.

Thus the claims are broadly drawn, encompassing almost any "marker", with no evidence that they would actually correlate to "angiogenesis modulation", particularly in vitro. The state of the art of drug dosage and determination is complex and unpredictable, with many factors which complicate the effective determination of a dose. Therefor one of skill in the art would not be enabled to practice the invention commensurate in scope with the claims.

Claim Rejections - 35 U.S.C. § 103

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are

such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

8. Claims 1-6, 9-18, 23-24, and 28 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ullrich et al., US Patent 6,177,401, published January 23, 2001, in view of Hirth, US Patent 5,942,385, and further in view of Fingl and Woodbury, The Pharmacological basis of Therapeutics, Chapter I, pages 25-33.

US Patent 6,177,401 teaches a method of screening, identifying and evaluating compounds which modulate angiogenesis, including angiogenesis related to cell proliferation (cancer), specifically the Flk-1 (a receptor involved in angiogenesis) antagonists, comprising administering the compound to a patient, monitoring a marker related to angiogenesis (protein phosphorylation), including comparing the marker to a standard, using an antibody based assay, and determining the efficacious dose based on the knowledge in the art, standard pharmaceutical techniques and a therapeutic index ratio (see for example, column 12, line 54-column 16, line 39, column 29, line 49-column 30, line 25, and column 23, lines 30-56).

US Patent 6,177,401 fails to teach a the administration of this monitoring assay to a patient, and determination of a correct drug dose using a standard curve.

US Patent 5,942,385 teaches that VEGF and flk-1 can be used to monitor cancer in patients, including in patients blood (which would inherently include monocytes) (see for example, column 6, lines 34-67).

Fingl and Woodbury teaches methods of determine efficacious drug dosages, including generating a standard curve.

Therefor it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to measure flk-1 activity (including protein phosphorylation), and further calculate a drug dose using the drug dosage standard curve of Fingl and Woodbury, and one would have been motivated to do so because flk-1 activity (including protein phosphorylation) correlates to drug efficacy, as taught in 6,177,401, and can be easily measured in numerous body fluids, including blood, as taught in 5,942,385, and because the dosage standard curves were the art standard way of determine an appropriate drug dose.

9. Claims 1-18, 23-24, and 28 are rejected under 35 U.S.C. 103(a) as being unpatentable over Tang et al., US Patent 5,792,783, published August 11, 1998, in view of Hirth, US Patent 5,942,385, and further in view of Fingl and Woodbury, The Pharmacological basis of Therapeutics, Chapter I, pages 25-33.

US Patent 5,792,783 teaches a method of screening, identifying and evaluating compounds which modulate angiogenesis, including angiogenesis related to cell proliferation (cancer), specifically the Flk-1 (a receptor involved in angiogenesis) antagonist SU 5416 (which is the instant compound a of claim 8), comprising administering the compound to a patient, monitoring a marker related to angiogenesis (protein phosphorylation) using an antibody based assay, and determining the efficacious dose based on the knowledge in the art, standard

pharmaceutical techniques and a therapeutic index ratio (see for example, column 2, line 63-column 3, line 40, column 13, lines 5-line 37, column 17, line 65-column 18, line 60, column 22, lines 59-67, and column 32, line 32-column 34, line 44).

US Patent 5,792,783 fails to teach a the administration of this monitoring assay to a patient, and determination of a correct drug dose using a standard curve.

US Patent 5,942,385 teaches that VEGF and flk-1 can be used to monitor cancer in patients, including in patients blood (which would inherently include monocytes) (see for example, column 6, lines 34-67).

Fingl and Woodbury teaches methods of determine efficacious drug dosages, including generating a standard curve.

Therefor it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to measure flk-1 activity (including protein phosphorylation), and further calculate a drug dose using the drug dosage standard curve of Fingl and Woodbury, and one would have been motivated to do so because flk-1 activity (including protein phosphorylation) correlates to drug efficacy, as taught in 5,792,783, and can be easily measured in numerous body fluids, including blood, as taught in 5,942,385, and because the dosage standard curves were the art standard way of determine an appropriate drug dose.

10. Claims 1-18, 23-24, and 28 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ullrich et al., US Patent 6,177,401, published January 23, 2001, in view of Hirth, US Patent

5,942,385, and further in view of Fingl and Woodbury, The Pharmacological basis of Therapeutics, Chapter I, pages 25-33.

US Patent 6,177,401 teaches a method of screening, identifying and evaluating compounds which modulate angiogenesis, including angiogenesis related to cell proliferation (cancer), specifically the Flk-1 (a receptor involved in angiogenesis) antagonists, comprising administering the compound to a patient, monitoring a marker related to angiogenesis (protein phosphorylation) using an antibody based assay, and determining the efficacious dose based on the knowledge in the art, standard pharmaceutical techniques and a therapeutic index ratio (see for example, column 12, line 54-column 16, line 39, column 29, line 49-column 30, line 25, and column 23, lines 30-56).

US Patent 6,177,401 fails to teach administration of this monitoring assay to a patient, the specific Flk-1 antagonist SU 5416, and determination of a correct drug dose using a standard curve.

US Patent 5,942,385 teaches that VEGF and flk-1 can be used to monitor cancer in patients, including in patients blood (which would inherently include monocytes) (see for example, column 6, lines 34-67).

US Patent 5,792,783 teaches a method of screening, identifying and evaluating compounds which modulate angiogenesis, specifically the Flk-1 antagonist SU 5416 (which is the instant compound a of claim 8), comprising administering the compound to a patient, monitoring a marker related to angiogenesis (protein phosphorylation) using an antibody based

assay, and determining the efficacious dose based on the knowledge in the art, standard pharmaceutical techniques and a therapeutic index ratio (see for example, column 2, line 63-column 3, line 40, column 13, lines 5-line 37, column 17, line 65-column 18, line 60, column 22, lines 59-67, and column 32, line 32-column 34, line 44).

Fingl and Woodbury teaches methods of determine efficacious drug dosages, including generating a standard curve.

Therefor it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to use the specific Flk-1 antagonist of US Patent 5,792,783, or the drug dosage standard curve of Fingl and Woodbury with the dosage assay of US Patent 6,177,401, and one would have been motivated to do so because the drug SU 5416 is a known Flk-1 antagonist, as taught by US 5,792,783, and because the dosage standard curves were the art standard way of determine an appropriate drug dose. Further one would have been motivated to administer such to a patient because flk-1 activity (including protein phosphorylation) correlates to drug efficacy, as taught in 5,792,783.

11. Claims 1-18, 23-24, and 28-31 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ullrich et al., US Patent 6,177,401, published January 23, 2001, in view of Hirth, US Patent 5,942,385, and further in view of Fingl and Woodbury, The Pharmacological basis of Therapeutics, Chapter I, pages 25-33.

US Patent 6,177,401, US Patent 5,792,783, US Patent 5,942,385, and Fingl and Woobury teach as set forth supra. US Patent 6,177,401, US Patent 5,792,783, US Patent 5,942,385, and Fingl and Woobury fail to teach that the specific efficacious dosages and standard curves.

Determination of specific optimal standard dosages/standard curves represents optimization of the known dosage curve methods and would be a matter of routine experimentation, given what is known in the art, exemplified in US Patent 6,177,401, US Patent 5,792,783, US Patent 5,942,385, and Fingl and Woobury.

Therefor it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was alter the methods of US Patent 6,177,401, US Patent 5,792,783, US Patent 5,942,385, and Fingl and Woobury to generate the specific standard curves of the instant claims and one would have done so as means of determining the most effective dose, based on the teachings and knowledge in the prior art.

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jennifer Hunt, whose telephone number is (703) 308-7548. The examiner can normally be reached Monday through Thursday 6:30am to 5:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa can be reached at (703) 308-3995. The fax number for the group is (703) 305-3014 or (703) 308-4242.

Communications via internet e-mail regarding this application, other than those under 35 U.S.C. 132 or which otherwise require a signature, may be used by the applicant and should be addressed to [**anthony.caputa@uspto.gov**].

All internet e-mail communications will be made of record in the application file. PTO employees do not engage in Internet communications where there exists the possibility that sensitive information could be identified or exchanged unless the record includes a properly signed express waiver of the confidentiality requirements of U.S.C. 122. This is more clearly set forth in the Interim Internet Usage Policy published in the Official Gazette of the Patent and Trademark on February 25, 1997 at 1195 OG 89.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the group receptionist, whose telephone number is (703) 308-0196.

Jennifer Hunt

November 5, 2001

ANTHONY C. CAPUTA
SUPERVISORY PATENT EXAMINER
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